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TITLE: A Phase I/II Trial of 13-Cis Retinoic Acid, Alpha Interferon, Taxotere, and Estramustine (R.I.T.E.) for the Treatment of Hormone Refractory Prostate Cancer

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**13. ABSTRACT (Maximum 200 Words)**
Advanced prostate cancer is only temporarily controlled with androgen ablation therapy. In order to overcome tumor resistance, we developed a epithelial cell line model to dissect out important mechanisms of resistance such as mutations in p53 and bcl-2 overexpression. In an attempt to sensitize these cells to paclitaxel (TAX), we found that 13-cis retinoic acid and alpha interferon (CRA/IFN) was capable of overcoming bcl-2 mediated resistance and reduced the expression of bcl-2 in human prostate cancer cells. We hypothesized that drugs, which could overcome bcl-2 mediated resistance, would improve chemotherapy response or duration of response in the clinic. We then translated these results to the clinic in a series of clinical trials. Recently, our phase II study with CRA/IFN/TAX was acceped as a National trial and is ongoing in the Eastern Cooperative Oncology Group. Given recet studies demonstrating that the combination of estramustine and docetaxes (ET) has increased response against HRPC in the clinic, but limited median duration of response, and our studies of CRA/IFN in the laboratory and clinic, we hypothesized that CRA/IFN will improve the response rate, or duration of response, of ET in patients with HRPC. We will treat patients with HRPC with R.I.T. E. therapy in a phase I and II trial.

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**INTRODUCTION:**

Advanced prostate cancer is only temporarily controlled with androgen ablation therapy. The use of chemotherapy is also limited with a median duration of response of only 5-6 months in all known regimens, secondary to the genomic instability of prostate cancer and subsequent development of tumor resistance. For example, one of the most active, and most utilized, combinations against HRPC is estramustine and taxotere with a 60% response rate, but a median duration or response of only 6 months. In order to overcome tumor resistance, we developed a pre-clinical epithelial cell line model to dissect out important mechanisms of resistance such as mutations in p53 and *bcl-2* overexpression, which increase with progression of tumors and development of resistance. This model was derived from primary baby rat kidney epithelial cells (BRK) transfected with genes encoding the murine temperature sensitive p53(val135) and a *bcl-2* expression vector. In an attempt to sensitize these cells to paclitaxel (TAX), we found that 13-cis retinoic acid and alpha interferon (CRA/IFN) was capable of overcoming bcl-2 mediated resistance and reduced the expression of bcl-2 in human prostate cancer cells. We hypothesized that drugs, which could overcome bcl-2 mediated resistance, would improve chemotherapy response or duration of response in the clinic. We then translated these results to the clinic in a series of clinical trials. In a pilot clinical trial using CRA/IFN alone in patients with prostate cancer, we demonstrated safety and activity in some patients. In a phase I trial, CRA/IFN in combination with TAX was well tolerated, had clinical activity, and reduced bcl-2 expression in peripheral blood mononuclear cells (PBMCs), which we studied as a potential biological marker of drug effect. Recently, our phase II study with CRA/IFN/TAX was accepted as a National trial and is ongoing in the Eastern Cooperative Oncology Group. Additional laboratory studies demonstrated that CRA/IFN decreased cell viability with regimens more commonly used for HRPC including estramustine/taxotere. Given recent studies demonstrating that the combination of estramustine and taxotere (ET) has increased response against HRPC in the clinic, but limited median duration of response, and our studies of CRA/IFN in the laboratory and clinic, we hypothesized that CRA/IFN will improve the response rate, or duration of response, of ET in patients with HRPC. We will treat patients with HRPC with R.I.T.E. therapy in a phase I and II trial. We will assess bcl-2 expression as a biological marker of effect in PBMCs and in tumor in patients.

Our specific aims are:

1. To conduct phase I/II trial of CRA/IFN with taxotere and estramustine (R.I.T.E) in patients with HRPC to determine the maximal tolerated dose, clinical response, and duration of response.
2. To determine the effect of R.I.T.E therapy on bcl-2 in PBMCs and tumor.

**BODY:**

Based on our prior data, as noted above, we hypothesized that CRA/IFN will improve the response rate, or duration of response, of ET in patients with HRPC, and developed a phase I and II study. Although this report covers the period of 2/15/03 to 2/14/04, the project was delayed in starting secondary to required approvals and revisions of the clinical trial. As requested, we submitted the clinical trial to the Surgeon General's Human Subjects Research Review Board (HSRRB) and obtained approval on 10/7/2002. Following the approval, the approved version of the trial and consent was submitted to our IRB and required amendment, which was approved 1/3/03. Personnel were hired and the trial opened to accrual 3/03. We have now reached our dose limiting toxicity (fatigue) in two patients in cohort 4 and will complete the phase I part of the study when an additional 3 patients are enrolled in cohort 3. Overall, 11 patients were enrolled. Patients received retinoic acid, 1 mg/kg, on days 1-4, interferon, six million units/m2 on days 1-4, estramustine, 280mg, orally three times a day on days 1-5, with escalating doses of docetaxel (0, 40, 50, 60mg/m2) on day 2, all repeated every 21days. Each patient had peripheral blood mononuclear cells (PBMCs) obtained prior to therapy and on days 2-4 of the first cycle of therapy to assess the effect of therapy on Bcl-2 by immunoblot. Currently, 10 patients were assessable for response (Nine with HRPC). Nine of 10 patients assessed to date had also progressed on prior chemotherapy. PSA decreased in 9/9 patients with HRPC in the ongoing phase I study (mean decrease of 35%). A PSA decrease of $\geq$ 50% was seen in 2/9 patients. Therapy was well tolerated in the phase I part of this study. Grade 3 fatigue occurred in the first cycle of 2 patients in cohort 4, defining a DLT, and in 3 additional patients beyond the first cycle. Fatigue resolved with dose reduction of interferon, as planned per study. Grade 3 hypophosphotemia transiently occurred after the first cycle of therapy in 2 patients in cohort 2 and 1 patient in cohort 3. Grade 3 nausea/vomiting occurred in 2 patients, in cohorts 1 and 3, beyond the first cycle. Grade 4 neutropenia occurred in 2 patients, without fever. Grade 3 hyperbilirubinemia was transiently seen in 1 patient in cohort 3. PBMCs were collected at baseline and day 2-4 for assessment of Bcl-2 expression. To date, we conclude that RITE therapy is well tolerated and active in this ongoing phase I/II study. Following full determination of the MTD in the phase I part of the study, a phase II study in patients with HRPC will be completed. Assessment of RITE effect on PBMC Bcl-2 expression is ongoing. An abstract of data for this portion of the study has been submitted to the American Society of Clinical Oncology for presentation at the June 2004 meeting. To date we have had no serious adverse events and the following timeline for our approved statement of work has begun:

Task 1: <u>To determine the safety and maximal tolerated dose of R.I.T.E. therapy</u>.

A. Treat patients with R.I.T.E. with dose escalations to determine the MTD (First 12 months).
B. Begin to assess peripheral blood and tumor when available for bcl-2, bclXL, bax and other apoptotic proteins by Western analysis (12 months). Store additional tumor for future 2D gel and DNA microarray.

Task 2: <u>To determine the response rate and duration of response of the regimen R.I.T.E. in HRPC</u>.

A. Complete phase II portion of the trial based on the dose obtained in the phase I portion of the trial, with assessment of PSA and tumor response (To begin in year 2, 3/04-3/05).
B. Assess response after the first 14 patients to determine if this regimen is active. If active, 30 patients will be accrued at the phase II dosing (Year 2 to 3, 3/04-3/06).

Task 3: <u>Assess PBMCs and tumor for bcl-2</u>.

A. Perform Western analysis on tumor and PBMCs for bcl-2 and other apoptotic proteins (Years 2-3).
B. Make preliminary analysis on possible correlations in effect on PBMCs and response with Dr. Shih.
C. Assess response and duration with Dr. Shih to determine the number of patients needed to complete future phase III trials comparing RITE with TE (Year 3).

**KEY RESEARCH ACCOMPLISHMENTS**

Full approval of the phase I and II clinical trial
Initiation of patient enrollment with near completion of phase I part of the study and submission of abstract to the American Society of Clinical Oncology.

**REPORTABLE OUTCOMES:**

PASCO 2004 abstract, as noted above.

**CONCLUSIONS:**

As planned, we have obtained approval and initiated the clinical study, with near completion of the phase I part of the study, and submission of initial data to the American Society of Clinical Oncology for 2004 presentation. The timeline initially changed, as noted in the report dated 3/13/03, given time required for study approval. Since this last report, accomplishments have been obtained as per the timeline in the statement of work. Completion of the phase II study and laboratory correlates will continue now in year 2 (2/14/04-2/13/05) and year 3 (2/14/05-2/13/06), as planned.